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Preparation and Evaluation of Aripiprazole-Loaded pH-Modulated Solid Dispersion via Hot-Melt Extrusion Technology

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PREPARATION AND EVALUATION OF ARIPIPRAZOLE-LOADED pH-MODULATED SOLID DISPERSION VIA HOT-MELT EXTRUSION TECHNOLOGY

by
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ABSTRACT
HALEY MCFALL: Preparation and Evaluation of Aripiprazole-Loaded pH-Modulated Solid Dispersion via Hot-Melt Extrusion Technology
(Under the direction of Dr. Dongwuk Kim)

The objective of this study was to prepare aripiprazole (ARI)-loaded solid dispersions (SDs) to enhance solubility and dissolution via hot-melt extrusion (HME) technology. ARI was chosen due to its poorly water-soluble properties. Solubility screenings of various polymers and acidifiers were performed to select appropriate excipients for the SD. Succinic acid (SA) and Kollidon 12 PF (PVP) were selected as the acidifier and the polymer, respectively. Differential scanning calorimetry and thermogravimetric analysis were used to determine the miscibility, interactions, and thermal stability of the drug and selected excipients. MODDE 8.0 is a design of experiment software that was implemented to produce several formulas that varied in screw speed and drug/polymer/acidifier ratios. The formulations were extruded using a twin-screw extruder and then milled into a fine powder using a laboratory grinder. Scanning electron microscopy and differential scanning calorimetry were used to perform solid-state characterizations of the pure drug and extrudates. The aqueous solubility and dissolution were then evaluated for the pure drug and milled extrudates. Each formulation showed increased solubility and dissolution compared to the crystalline ARI powder, which showed that HME is an advanced approach to enhance the dissolution and solubility of poorly soluble drugs. Since PVP was extrudable with ARI and SA, it appears to be a promising carrier for SDs with the poorly

water-soluble drug using HME. Furthermore, the addition of an appropriate acidifier to the formulation has an important role on the solubility and dissolution of drug. The pH-modulated SD via HME could be used as a platform technology for solubilization of various poorly water-soluble drugs with pH-dependent solubility.

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LIST OF ABBREVIATIONS

Ac-Di-Sol	croscarmellose sodium (excipient)
ARI	aripiprazole
BCS	biopharmaceutics classification system
DoE	design of experiment
DSC	differential scanning calorimetry
HME	hot-melt extrusion
IDP	isradipine
MCC	microcrystalline cellulose (excipient)
MS	magnesium stearate
pH_m	micro-environment pH
PM	physical mixture
PVP	Kollidon 12 PF
SA	succinic acid
SEM	scanning electron microscopy
SD	solid dispersion
TGA	thermogravimetric analysis

I. Introduction

Oral administration is the simplest and most common delivery method of drug dosage forms. Oral dosage forms are also safe and easy for a patient of any age to swallow. However, it is estimated that about 40% of the current immediate-release oral drugs on the market are basically insoluble in water (Kawabat *et al*., 2011). Therefore, one of the major challenges with oral dosages is their poor bioavailability. Poor bioavailability of a drug is most frequently a result of low solubility and low permeability. Consequently, drugs are classified based on their solubility and permeability properties according to the Biopharmaceutics Classification System (BCS). The BCS is comprised of four categories, which are as follows: high solubility/high permeability (class I), low solubility/high permeability (class II), high solubility/low permeability (class III), and low solubility/low permeability (class IV). In order to increase a drug's bioavailability, it is easier to enhance the solubility of a drug rather than its permeability. Therefore, most drugs are in the class II category (Lee *et al*., 2013) and are widely researched since only their solubility properties have to be manipulated to have better bioavailability. This study focuses on the class II drug aripiprazole (ARI) and preparing solid dispersions (SDs) via hot-melt extrusion (HME) technology to improve the bioavailability of ARI.

ARI (Fig. 1) is an atypical, antipsychotic drug administered to treat schizophrenia and bipolar disorder. ARI is currently sold on the market under the

trade name Abilify. Again, it is a BCS class II drug, meaning it has low solubility in water and poor bioavailability. ARI is also a weak alkaline drug with its solubility being pH-dependent in aqueous solutions. In this study, the addition of an acidifier to the SD was studied to determine the effect it had on the solubility of ARI. HME technology was employed to develop the SDs.

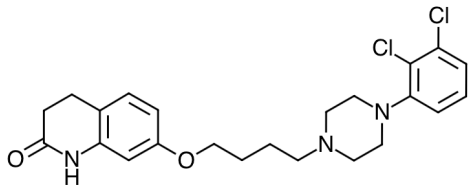


Figure 1. Structure of aripiprazole.

Acidifiers are considered to be an important component to maintaining the micro-environment pH (pH_m). Lower pH_m are necessary to enhance the drug dissolution for drugs that have a higher solubility in more acidic environments. However, extensive research on the incorporation of acidifiers in SD has not been conducted, but Tran *et al*. (2010) studied the effects of several acidifiers on SDs and physical mixture (PM). The SD and PM tablets in this study were created using the poorly water-soluble drug isradipine (IDP) and the polymer PVP with one of the following acids: fumaric acid, citric acid, glycolic acid, and malic acid. The pH_m of each acidifier was plotted over a time period of 15 minutes. Each acidifier proved to lower the pH_m when compared to the SD without any acidifier. The release rate profiles of the acidifiers and percent of drug released were plotted over a range of 60 minutes. Compared to the pure drug, all acidifiers improved the dissolution of IDP. It should be noted, though, that fumaric acid has the lowest release rate of acidifier and the highest dissolution rate of the drug (Tran *et*

al., 2010). These findings suggest slower release rates of acidifiers preserve the lower pH_m necessary for enhanced drug dissolution.

Various techniques are available to enhance the poor solubility of BCS class II drugs. Among those techniques that have been successful are nanoparticle formation, particle size reduction, salt formation, complexation with hydrophilic substances, and solid dispersion. SDs have shown to be one of the must successful ways to enhance the solubility and therefore, dissolution of drugs (Vasconcelos *et al*., 2007). SDs are the dispersion of a drug in an inert hydrophilic carrier or polymer matrix. SDs alter the state of the crystalline drug to an amorphous form, which improves the dissolution of the drug (Tran *et al*., 2010). In this study, the SDs were prepared using hot-melt extrusion technology.

HME technology has been used widely in the plastics industry for around 70 years but has only gained interest in the pharmaceutical industry in the last two decades (Repka *et al*., 2011). HME is applied to prepare SDs in attempts to overcome the challenge of low bioavailability drugs. HME is a continuous process that operates under defined conditions. The following parameters can be varied in the HME process to achieve a consistent product: screw rotating speed, rate of the feed materials, temperature, and shear (Repka *et al*., 2011). Raw materials are fed to through a heated barrel, containing rotating screws that are divided into different zones for mixing and conveying. The materials are also melted and plasticized as they travel the length of the barrel. Several of the advantages to using HME technology are short processing time, continuous process, solvent-free, and scalable process (Repka *et al*., 2011). HME has

shown to be successful in improving the bioavailability because of the uniformity in drug dispersion of the final product.

Currently, there is a lack of information about the roles of acidifiers in SDs. Since many drugs are pH-dependent, this study provides insight on the importance of acidifiers in the SD in order to enhance bioavailability. Also, only a few drugs on the market are now being produced using HME technology. As this method gains popularity in the pharmaceutical industry, more research is needed on the possibility of SDs being produced by HME technology. This study not only discusses the incorporation of acidifiers in SDs but also the preparation of SD using HME technology.

II. Materials and Methods

2.1 Materials

Aripiprazole (melting point at 137-142°C) was kindly provided by Hanyang University (Ansan, South Korea). Acidifiers (adipic acid, citric acid, fumaric acid, malic acid, maleic acid, stearic acid, succinic acid, and tartaric acid) were purchased from Spectrum Quality Products, Inc. (Gardena, CA, USA). Kollidon 12 PF and Soluplus were generously supplied by BASF Corporation (Florham Park, NJ, USA). Aquasolve HPMCAS-LG, Klucel EXF, Benecel E15, Benecel K15M, and Natrosol 250L were gifted by Ashland, Inc. (Lexington, KY, USA). All other chemicals used were reagent grade and were used without further purification.

2.2 Solubility screening of the acidifiers and polymers

The acidifiers and polymers listed above were screened to select the appropriate components for the SD. The samples contained 15 mL of ionized water and 150 mg of acidifier or polymer to make 1% aqueous solutions. Excess amount of ARI was added to 2.0 mL microtube carrying 1.2 mL of each aqueous solution. The aqueous solutions were vortexed vigorously and placed in a shaking water bath at 100 rpm and 37°C for five days. Then, they were centrifuged for 10 minutes at 25°C and 13.2k rpm to separate the undissolved ARI. The supernatant solutions were filtered and diluted with distilled water for quantification of ARI by an UV-Vis spectrophotometer (Genesys 6, Thermo

Scientific, USA). The absorbance was measured at 217 nm with spectrophotometer against distilled water as a blank. All tests were repeated in triplicates.

2.3 Pre-formulation thermal analysis (DSC and TGA)

The miscibility, interaction and thermal stability of ARI, succinic acid (SA), Kollidon 12 PF (PVP), and physical mixture (PM, 1:1:1 weight ratio) were analyzed using DSC (Perkin Elmer Diamond DSC) and TGA (Perkin Elmer Pyris 1 TGA) instruments. For the DSC, all samples weighed about 5 mg and were sealed in an aluminum pan. An empty aluminum pan was used as a reference. The samples were heated under nitrogen gas for one minute at 25°C and then heated to 200°C at a rate of 10°C per minute. The thermal stability of the components and the PM was evaluated using TGA over the temperature range of 60°C to 220°C. About 3-4 mg of samples were placed in an aluminum crucible and heated at 10°C per minute under a controlled atmosphere of nitrogen. Percent weight loss was plotted against temperature to determine weight loss.

2.4 Preparation of pH-modulated solid dispersions and tablets

ARI (20-40% w/w), PVP (60-80% w/w) and SA (0-10% w/w) were blended using a V-shell blender (Maxiblend, GlobePharma) and extruded at 120°C using a twin-screw extruder (Process 11, Thermo Fisher Scientific). The screw speed was set at 80-120 rpm. Then, each extrudate was milled into a fine powder using a laboratory grinder. For the tablets, MCC, Ac-Di-Sol, and MS were chosen as the excipients in a weight ratio of 90:9:1, respectively. A combined 300 mg of formulation and excipients were compressed

to make tablets for the dissolution study. Each tablet contained 30 mg of drug, which is comparable to the amount of drug in the commercialized product.

2.5 Solubility and dissolution

The aqueous solubility and dissolution rates were evaluated for the milled extrudates and the pure drug. For the solubility study of the formulations, an excess amount of the formulation was added to 1.2 mL of distilled water. The samples were then placed in a sonication machine to ensure complete mixing. The samples were made in triplicates and placed in a shaking water bath at 37°C and 100 rpm for five days. Then, they were centrifuged for 10 minutes at 25°C and 13.2k rpm. The absorbance of each sample was evaluated using UV spectroscopy. The tablets were placed in 900 mL of water at 37.5°C for determination of the dissolution rates of the tablets. The paddle method was employed with a rate of 75 rpm. A sample of the medium was extracted for each tablet at 5, 10, 15, 20, 30, 45, and 60 minutes to determine the dissolution rate.

2.6 Solid state characterizations

Scanning electron microscopy (SEM) and DSC were used to perform solid-state characterizations of the pure drug and extrudates. SEM (JSM-5600 SEM) was used to explore the shape and surface morphology of ARI, SA, PVP, and each formulation. For DSC, around 5 mg of formulation for each sample was sealed in an aluminum pan and compared to an empty pan. The samples were heated at 25°C for one minute before being heated to 200°C at a rate of 10°C per minute. Nitrogen gas was used in the DSC analysis.

2.7 Design of experiment

MODDE 8.0 was the design of experiment software applied to identify the effect of screw speed and drug/polymer/acidifier ratio on solubility and dissolution. It used a 2^3 full factorial design to provide 11 formulations that varied the drug content from 20% to 40%, the acidifier content from 0% to 10%, and the polymer content from 60% to 80%. The screw speed of the extrusion process was also varied from 80 to 120 rpm. The results of the DoE formulations are shown in Table 1.

Table 1. DoE formulation results.

Formulation Name	Screw Speed (rpm)	Drug Content (%)	Acidifier Content (%)
N1	80	20	0
N2	120	20	0
N3	80	40	0
N4	120	40	0
N5	80	20	10
N6	120	20	10
N7	80	40	10
N8	120	40	10
N9	100	30	5
N10	100	30	5
N11	100	30	5

III. Results and Discussion

3.1 Pre-formulation solubility screening

ARI, a weakly basic drug, has been shown to have a pH-dependent solubility. Preliminary studies show that ARI has higher levels of drug solubility in more acidic environments. Figure 2 shows that ARI was most soluble at pH values of 1.2 and 4.0 and had very low solubility in pH solutions above 6.8. Appropriate acidifying agents and hydrophilic polymers were screened to improve the solubility and dissolution of ARI.

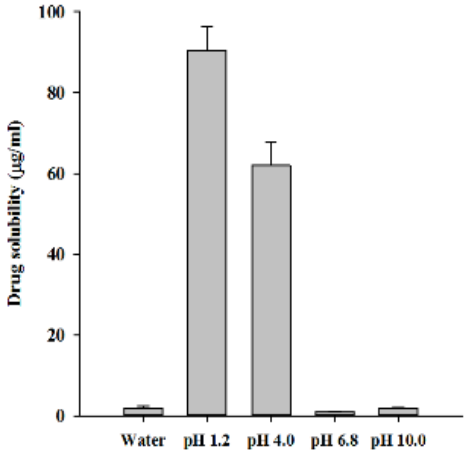
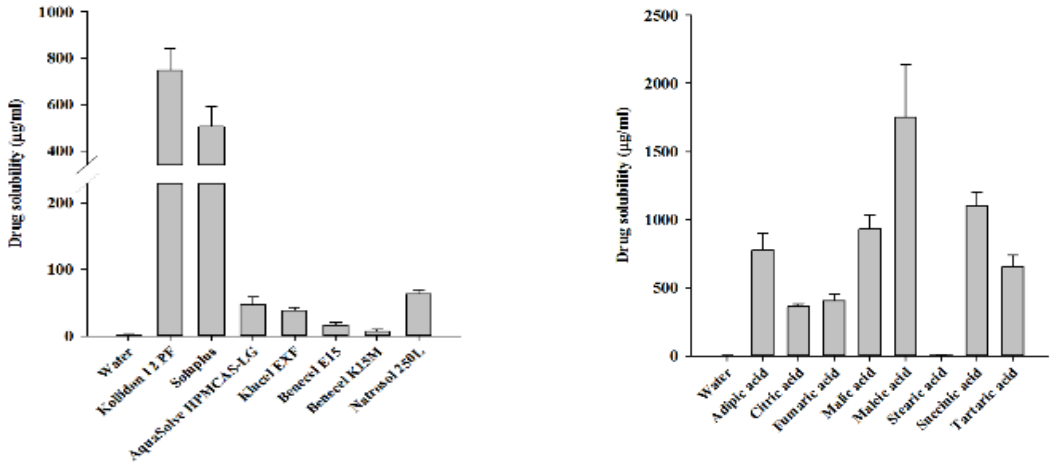


Figure 2. Solubility of ARI in different pH solutions.

The various polymers and acidifiers were prepared as 1% aqueous solutions to test the drug solubility in each solution. UV spectroscopy was employed to evaluate the solubility of ARI in each polymer and acidifier. The samples were analyzed at 217 nm

which was the wavelength used in a study by Fousteris *et al.* (2013). Figure 3A shows that ARI had the highest amount of solubility in Kollidon 12 PF (PVP), which was chosen as the polymer for this study. Figure 3B shows that the highest level of drug solubility was when ARI was mixed with maleic acid. However, at low temperatures, maleic acid showed to have stability issues. Therefore, succinic acid was chosen as the acidifier since ARI had the second highest level of solubility in SA.



(A) (B)

Figure 3. Solubility of ARI in various polymers (A) and acidifiers (B).

3.2 DSC and TGA of formulation components

The thermal stabilities of ARI, SA, PVP, and PM were analyzed using DSC and TGA techniques. These techniques can provide information about the decomposition, melting, recrystallization, or change in specific heat capacity for each component (Marasini *et al.,* 2013). The curves for each component in the DSC are shown in Figure 4. ARI has a peck around 140°C, which corresponds to its melting point. The PVP displays a horizontal line over the temperature range analyzed, indicating it has a melting

temperature greater than 200°C. Succinic acid shows to have a melting point around 190°C. The physical mixture has a small peak around 140°C, which correlates with the melting temperature of ARI. This peak indicates that as the components in the PM are heated, there are not interactions between the ARI, SA, and PVP.

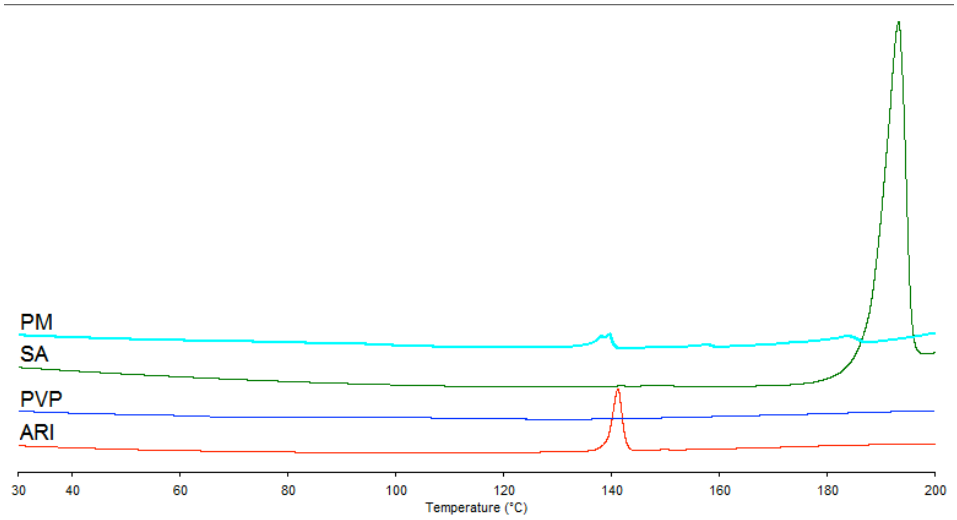


Figure 4. DSC curves for ARI, PVP, SA, and PM

TGA was used to determine the decomposition of the components from 60°C to 220°C. In Figure 5, the ARI and SA curves show consistent weight percentage over the temperature range, meaning there is no decomposition of these components. Both the PVP and PM have similar curves with about 5% decrease in the weight percent (Figure 5). This decrease is due to the fact that the PVP contains some water content, so at the lower temperature, the water is being evaporated.

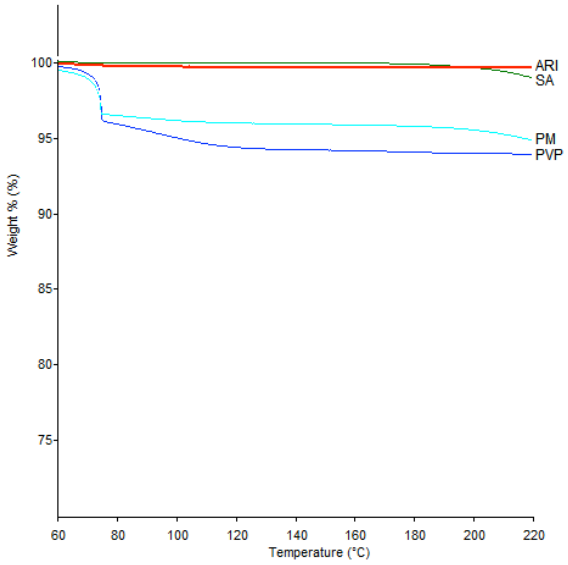


Figure 5. TGA curves for ARI, PVP, SA, and PM.

3.3 Hot-melt extrusion technology

MODDE 8.0 design of experiment software was employed to develop several formulations that varied in screw speed and drug/acidifier/polymer content to investigate these effects on the solubility and dissolution of ARI. The results from the computation are provided in Table 1. The formulations were extruded at 120°C because this was the lowest temperature at which they could be extruded. Lower temperatures are more likely to a produce a product with more physical stability. Figure 6 illustrates the physical differences in each of the formulations. N1-2 and N5-6 contain 20% of ARI while N3-4 and N7-8 contain 40% of ARI. N1-4 contain no acidifier while N5-8 contain 10% of acidifier. N9-11 all contain 30% ARI and 5% SA. Figure 6 shows that the varying content of ARI, SA, and PVP changes the coloring of the extrudates.

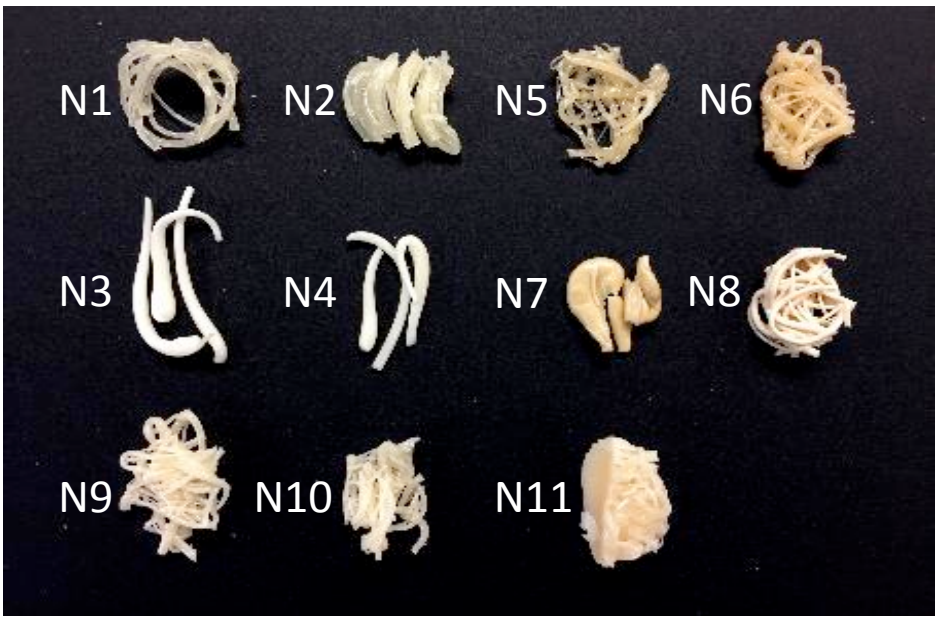
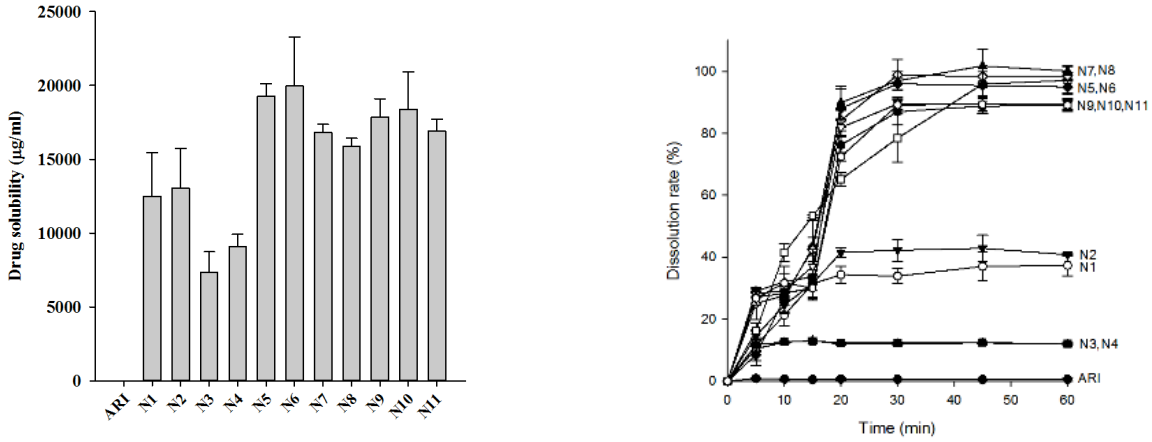


Figure 6. Image of the formulations after the HME process.

3.4 Solubility and dissolution of the formulations

All formulations showed improved levels of solubility and dissolution compared to the pure drug (Figure 7). In Figure 7A, the formulations that contained some acidifier (N5-11) had greater solubility of ARI than the formulations that did not contain any acidifier (N1-4). N5 through N11 have relatively close levels of drug solubility when the errors bars are taken into account. The results are very similar for the dissolution study shown in Figure 7B. N5 through N11 formulations showed around 40% to 60% higher dissolution rates than N1 through N4. The dissolution rates for N5 through N11 are very similar for the first 20 minutes. After 20 minutes, there is some separation between these formulations, but they are all still relatively close.

The pH of the media was also taken after the dissolution study was completed and is displayed in Figure 8. All of the formulations with acidifier reduced the pH of the media to pH values of 4.5 – 5.5. Therefore, the acidifier lowers the pH of the media



(A) (B)

Figure 7. Solubility (A) and dissolution rates (B) of ARI in each formulation.

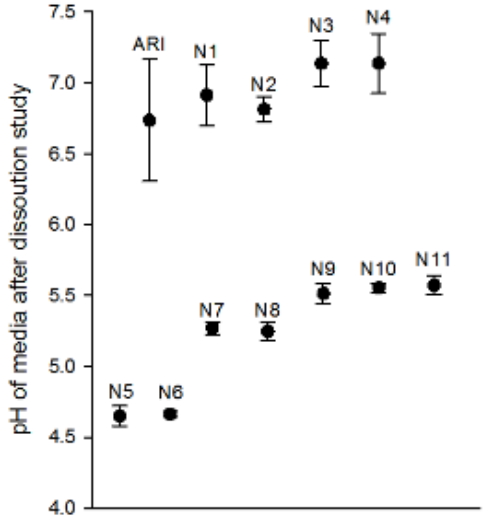


Figure 8. pH of the media after dissolution.

surrounding the tablet, which in turn increases the solubility and dissolution rate of ARI. This study demonstrates that the incorporation of an acidifier with pH-dependent drugs will enhance its solubility and dissolution rate.

3.5 DSC analysis of formulations

DSC was applied to the various formulations for analysis and comparison to the components separately. Each curve for the formulations is a relatively horizontal line. Since there are not any peaks for the formulations, it can be inferred that each formulation has been transformed into the amorphous state. This change of state would further indicate why the formulations had higher solubility and dissolution rates compared to the crystalline drug.

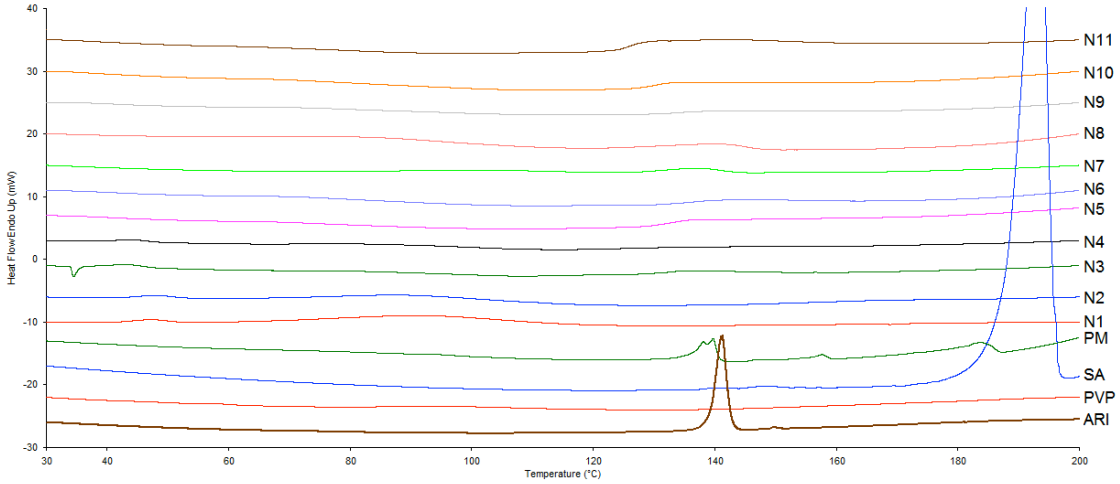
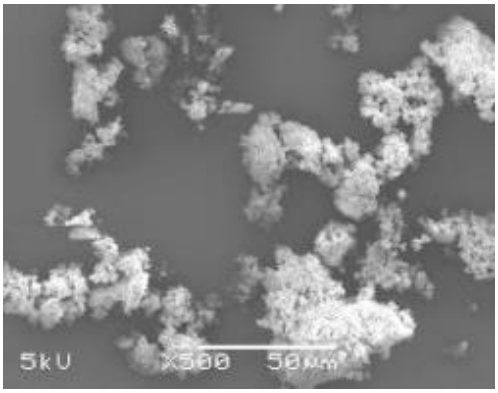


Figure 9. DSC curves for each formulation.

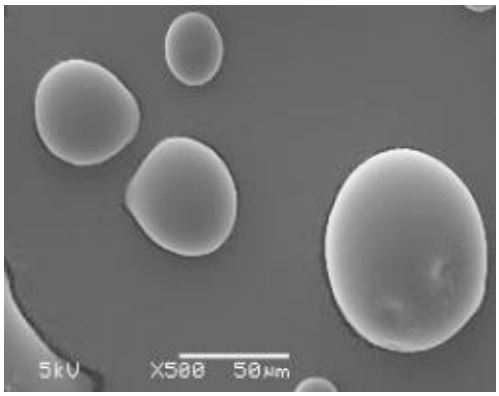
3.6 Morphological characterization

SEM images were obtained of ARI, SA, PVP, and N9 to observe the surface of each of these (Figure 10). ARI appeared as irregular crystals with a rough surface while the PVP and SA both appear at spherical particles with moderately smooth surfaces. The N9 extrudate shows a smooth surface. The milled N9 extrudate are also smooth-surface,

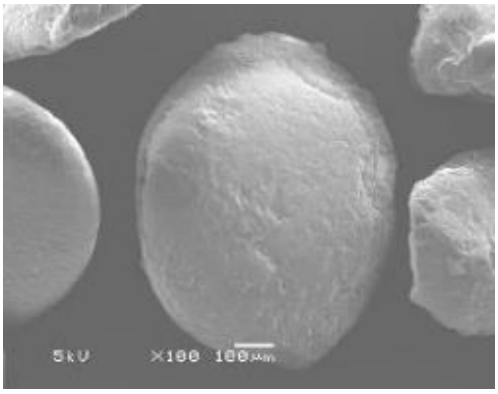
spherical particles. Solid-state characterization further demonstrates the transformation of crystalline ARI to an amorphous state.



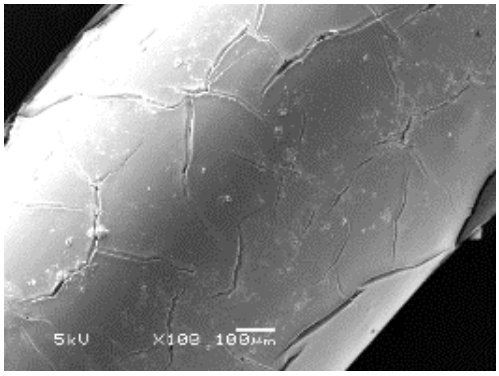
(A)



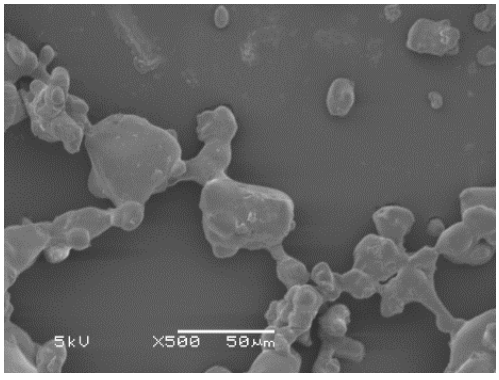
(B)



(C)



(D)



(E)

Figure 10. SEM images of ARI (A), PVP (B), SA (C), N9 surface (D), and milled N9 (E).

3.7 Design of Experiment and response surface

The DoE was used to investigate the effects screw speed, drug content, and acidifier content had on the dissolution at 30 minutes and 60 minutes, solubility, and pH. The DoE used the following model equation to calculate these effects:

$$y = a_1x_1 + a_2x_2 + a_3x_3 + a_{12}x_1x_2 + a_{23}x_2x_3 + a_{13}x_1x_3 + b \qquad \text{(eq. 1)}.$$

The first three terms are the effects of screw speed, drug content, and acidifier content, respectively. The fourth term is the effect of screw speed and drug content while the fifth term is the effect of screw speed and acidifier content. The last term is the effect of drug and acidifier content. The statistical effects of these variables are displayed in Table 2. The outputs, y_n, are dissolution at 30 minutes, dissolution at 60 minutes, solubility, and pH, respectively. To determine which variable impacts the output the most, the magnitude of each term is taken. For the dissolution at 30 minutes (y_1), the acidifier content (a_3x_3) has the greatest effect. This is also true for the dissolution at 60 minutes (y_2). Since the value is positive for these terms, the dissolution will increase as the acidifier content increases. For the solubility (y_3) and pH (y_4), the drug content (a_2x_2) and acidifier content (a_3x_3), separately, greatly impact the outputs. For the solubility output and drug content term, the value is negative, indicating that the solubility decreases with increasing drug content. The value is positive for the solubility output and acidifier content term, which means the solubility will increase with increasing acidifier. The opposite is true for the pH output. The value is positive for the pH output and drug content term, so the pH increases with increasing drug content. However, the pH decreases with increasing acidifier. Since the drug is alkaline and the acidifier was shown in lab to lower the pH, these correlations make sense.

Table 2. DoE statistical results.

	a_1x_1	a_2x_2	a_3x_3	$a_{12}x_1x_2$	$a_{23}x_2x_3$	$a_{13}x_1x_3$	b	R^2	p
y_1	3.04	-3.79	33.71	-3.44	0.89	9.12	66.95	0.84	0.126
y_2	0.39	-5.96	36.09	0.03	-0.51	7.61	69.11	0.87	0.084
y_3	254.58	-1963.66	3747.09	-52.92	-317.50	324.64	15178.3	0.84	0.129
y_4	-0.01	0.22	-1.02	0.01	0.01	0.08	5.86	0.96	0.004

The R^2 value is an indication of how closely the data fits the model. The closer this value is to 1, the better fitted the data is to the model. Since the R^2 values in Table 2 are fairly close to 1, the model is acceptable for the data. The p-value determines if the model is statistically significant or not. Typically, it is considered statistically important if p is less than 0.05. However, this particular software suggests that it is statistically important if p is less than 0.2. Each of the models above has a p-value less than 0.2, so each model is statistically significant.

The DoE was also used to produce visual representations of the effects the factors have on the outputs. These images are displayed in Figure 11. The screw speed only showed an effect on the dissolution at 30 minutes (Figure 11A). As the screw speed is increased, the dissolution rate at 30 minutes also increases. Figure 11B illustrates how the dissolution rate at 60 minutes increases with increasing amounts of acidifier. In Figure 11C, the solubility also increases with increasing amounts of acidifier. To produce Figure 11D, the screw speed was set to 100 rpm. The two criteria to meet were dissolution of 60% to 100% at 30 minutes (criteria 1) and dissolution of 90% to 100% at 60 minutes (criteria 2). Figure 11D shows the combinations of acidifier and drug content that will meet these criteria. The blue areas are the combinations of acidifier and drug content that

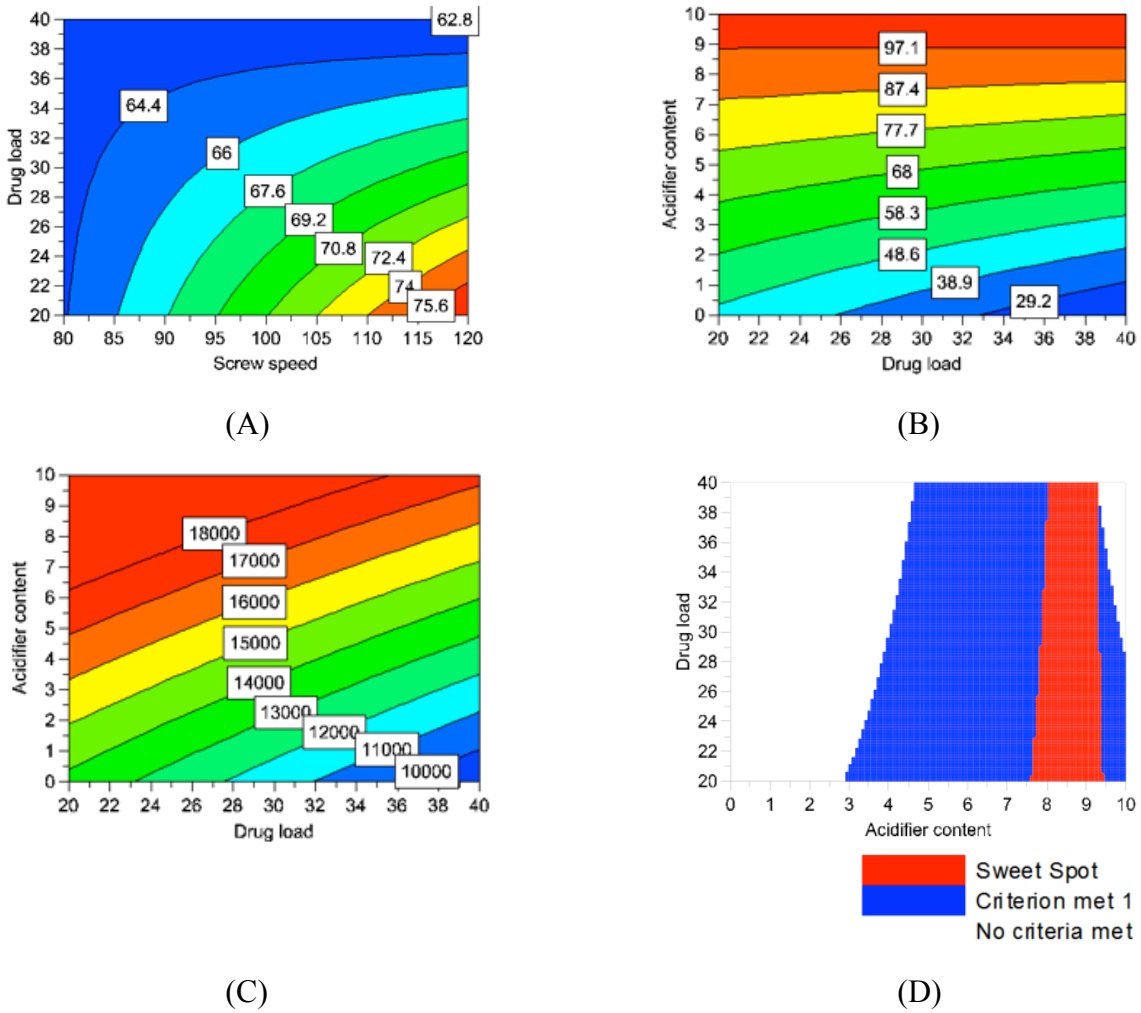


Figure 11. Response surfaces from the DoE. (A) Dissolution at 30 minutes. (B) Dissolution at 60 minutes. (C) Solubility. (D) Sweet spot conditions.

will meet criteria one. The red area, or the sweet spot, is the combinations of acidifier and drug content that will meet both criteria.

IV. Conclusion

There are few studies on the incorporation of acidifiers in SDs and producing the SD via HME technology in order to increase the solubility and dissolution of poorly water soluble drugs. This study focuses on improving the bioavailability of the BCS class II drug ARI using both an acidifier and HME technology. From the solubility screening, PVP and SA were chosen as the hydrophilic polymer and acidifying agent, respectively. The PVP was extrudable with SA and ARI at 120°C using HME. All formulations enhanced the solubility and dissolution when compared to the pure drug. However, the formulations containing some acidifier had even higher solubility and dissolution rates than the formulations that had no acidifier. The solubility and dissolution rates also correlated the pH of the media after dissolution. The formulations with acidifier proved to lower the pH_m and, therefore, had better solubility and dissolution. Solid-state characterizations revealed that the majority of the crystalline ARI had been transformed into an amorphous state. Overall, the addition of an acidifying agent to the formulation and the use of HME technology had a significant impact on the solubility and dissolution. The results of this study could be insightful for future studies on pH-modulated SD via HME technology.

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